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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/555,964	09/08/2000	Meir Shinitzky	24259	9351

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/555,964	SHINITZKY ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ ~~Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)~~ Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 6-13 are pending.

2. The following new grounds of rejection are necessitated by the amendment filed 1/6/04.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 6-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method of preparing a protein preparation or reagent for use in diagnosis of schizophrenia in an individual by detecting a DTH reaction in said individual following injection of said reagent to the individual, comprising: (a) obtaining blood samples from a number of individual, preparing a pool from said samples and collecting platelets therefrom; (b) preparing a protein fraction from said platelet preparation comprising proteins or fractions thereof wherein the pI of said proteins or fractions thereof is within the range of about 6.5 to about 9.5 and a diagnostic method for determining schizophrenia in a subject using said proteins or fractions wherein the pI of said proteins or fractions thereof is within the range of about 6.5 to about 9.5, **does not** reasonably provide enablement for a method for preparing a reagent for use in diagnosing schizophrenia and a method of diagnosing schizophrenia using proteins or fractions from platelet wherein the pI of the proteins or fractions is greater than or equal to about 6.5 as set forth in claims 6-13. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient

to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only method of preparing a protein preparation or reagent for use in diagnosis of schizophrenia in an individual by detecting a DTH reaction in said individual following injection of said reagent to the individual, comprising: (a) obtaining blood samples from a number of individual, preparing a pool from said samples and collecting platelets therefrom; (b) preparing a protein fraction from said platelet preparation comprising proteins or fractions thereof wherein the pI of said proteins or fractions thereof is within the range of about 6.5 to about 9.5 and a diagnostic method for determining schizophrenia in a subject using said proteins or fractions wherein the pI of said proteins or fractions thereof is within the range of about 6.5 to about 9.5.

The specification does not teach the claimed methods as set forth in claims 6-13 because there is insufficient guidance as how to make *any* platelet proteins or fractions thereof wherein the "pI is *greater than* or *equal to about* 6.5". The specification discloses that the pI of the platelets proteins fractions is within the range of about 6.5 to about 9.5 (pool 2 proteins). The term "greater than" renders the upper limits of the pI to infinity. There is insufficient guidance and in vivo working demonstrating that all proteins fractions having a pI greater than 6.5 such as 10 is effective for a diagnosing schizophrenia in a subject. Further, the specification does not disclose the platelets proteins or fractions equal to about 6.5 is effective for the claimed diagnostic method for determining schizophrenia in all subject. The term "about" expands the upper and lower limits of the pI. The specification discloses the diagnostic method does not work when the pI is lower than 6.5. In fact, the specification discloses that platelets proteins are divided into two separate groups in accordance with their pI: protein having a pI in the range of 2 to 6.5 are referred to as Pool 1 proteins while proteins having a pI in the range of 6.5 to 9.5 are referred to as Pool 2 proteins (page 12). A delayed type hypersensitivity reaction to Pool 2 proteins (pI within the range of 6.5 to 9.5) was observed in a schizophrenic patient and no DTH reaction to Pool 1 proteins (pI within the range of 2 to 6.5) at the site of injection (See page 13).

Further, not only there are more than one platelet proteins associated with any one specific pI, there is insufficient guidance as to the molecular weight of any platelet proteins associated with that particular pI, let alone the structure associated with function of any platelet proteins for the claimed diagnostic method. A platelet protein without the molecular weight associated with the specific amino acid sequence has no structure, much less function.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Applicants have not provided any biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies the various platelet proteins for the claimed method. While protein having a range of pI of above about 6.5 or a pI within the range of above 6.5 to about 9.5 may have some notion of the activity such as induces DTH, claiming a method of injecting platelet proteins fails to distinctly claim what that proteins are and what the compositions are made up of for the claimed method. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe nor enable any platelet proteins for the claimed diagnostic method other than the isolated platelet or platelet proteins fraction having a pI in the range of 6.5 to 9.5 as disclosed on page 12 of the specification.

Given the indefinite number of undisclosed platelet proteins having a pI of above about 6.5 or within the range of above 6.5 to about 9.5, it is unpredictable which undisclosed platelet proteins is useful for the claimed method of diagnosing schizophrenia in a subject. Therefore, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 1/6/04 have been fully considered but are not found persuasive.

Applicants' position is that claims 6-9 have been amended; the application does not claim an isolated protein because that is not the inventive subject matter. The identity of the precise agent which produces the DTH reaction is irrelevant. Applicants found that the fraction having a pI below about 6.5 has no activity, leading applicants to eliminate the range below about 6.5 from their claims, and leaving the range "above about 6.5". What is claimed is the fraction produced

by the inventive process, not a single component of that fraction. There is no issue of undue experimentation because there is no experimentation whatsoever required to practice the claimed method.

In response, the specification does not teach the claimed methods as set forth in claims 6-13 because there is insufficient guidance as how to make *any* platelet proteins or fractions thereof wherein the "pI is *greater than* or *equal to about* 6.5". The specification discloses that the pI of the platelets proteins fractions is within the range of 6.5 to 9.5 (pool 2 proteins). The term "greater than" renders the upper limits of the pI to infinity. There is insufficient guidance and in vivo working demonstrating that all proteins fractions having a pI greater than 6.5 such as 10 is effective for a diagnosing schizophrenia in a subject. Further, the term "equal to about 6.5" renders the range unclear. No where in the specification discloses the platelets protein fraction *equal* to 6.5 is effective for the claimed diagnostic method for determining schizophrenia in all subject. The term "about" expands the upper and lower limits of the pI. The specification discloses the diagnostic method does not work when the pI is lower than 6.5. In fact, the specification discloses that platelets proteins are divided into two separate groups in accordance with their pI: protein having a pI in the range of 2 to 6.5 are referred to as Pool 1 proteins while proteins having a pI in the range of 6.5 to 9.5 are referred to as Pool 2 proteins (page 12). A delayed type hypersensitivity reaction to Pool 2 proteins (pI within the range of 6.5 to 9.5) was observed in a schizophrenic patient and no DTH reaction to Pool 1 proteins (pI within the range of 2 to 6.5) at the site of injection (See page 13).

5. Claims 6-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of a method for preparing a reagent for use in diagnosing schizophrenia and a method of diagnosing schizophrenia using proteins or fractions from platelet wherein the pI of the proteins or fractions is "greater than or equal to about 6.5 as set forth in claims 6-13.

The specification discloses only method of preparing a protein preparation or reagent for use in diagnosis of schizophrenia in an individual by detecting a DTH reaction in said individual following injection of said reagent to the individual, comprising: (a) obtaining blood samples

from a number of individual, preparing a pool from said samples and collecting platelets therefrom; (b) preparing a protein fraction from said platelet preparation comprising proteins or fractions thereof wherein the pI of said proteins or fractions thereof is within the range of about 6.5 to about 9.5 and a diagnostic method for determining schizophrenia in a subject using said proteins or fractions wherein the pI of said proteins or fractions thereof is within the range of about 6.5 to about 9.5.

Other than the specific isolated platelet or platelet proteins fraction having a pI within the range of 6.5 to 9.5 for the claimed methods, there is insufficient written description about the structure associated with function of any platelet proteins or fractions wherein the pI is "*greater than* or equal to *about* 6.5". The specification discloses that the pI of the platelets proteins fractions is within the range of about 6.5 to about 9.5 (pool 2 proteins). The term "greater than" renders the upper limits of the pI to infinity. There is inadequate written description about all proteins fractions having a pI *greater than* 6.5 such as 10 is effective for a diagnosing schizophrenia in a subject. Further, the term "equal to about 6.5" renders the range unclear. No where in the specification discloses the platelets protein fraction *equal* to 6.5 is effective for the claimed diagnostic method for determining schizophrenia in all subject. The term "about" expands the upper and lower limits of the pI. In fact, the specification discloses that platelets proteins are divided into two separate groups in accordance with their pI: protein having a pI in the range of 2 to 6.5 are referred to as Pool 1 proteins while proteins having a pI in the range of 6.5 to 9.5 are referred to as Pool 2 proteins (page 12). A delayed type hypersensitivity reaction to Pool 2 proteins (pI within the range of 6.5 to 9.5) was observed in a schizophrenic patient and no DTH reaction to Pool 1 proteins (pI within the range of 2 to 6.5) at the site of injection (See page 13).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 1/6/04 have been fully considered but are not found persuasive.

Applicants' position is that claims 6-9 have been amended. Only if the application does not either described either an actual reduction to practice or other structural formula, should the examiner consider the sufficiency of the written description.

In response, other than the specific isolated platelet or platelet proteins fraction having a pI within the range of 6.5 to 9.5 for the claimed methods, there is insufficient written description about the structure associated with function of any platelet proteins or fractions wherein the pI is "*greater than* or *equal to about* 6.5". The specification discloses that the pI of the platelets proteins fractions is within the range of about 6.5 to about 9.5 (pool 2 proteins). The term "greater than" renders the upper limits of the pI to infinity. There is inadequate written description about all proteins fractions having a pI *greater than* 6.5 such as 10 is effective for a diagnosing schizophrenia in a subject. Further, the term "equal to about 6.5" renders the range unclear. No where in the specification discloses the platelets protein fraction *equal* to 6.5 is effective for the claimed diagnostic method for determining schizophrenia in all subject. The term "about" expands the upper and lower limits of the pI. In fact, the specification discloses that platelets proteins are divided into two separate groups in accordance with their pI: protein having a pI in the range of 2 to 6.5 are referred to as Pool 1 proteins while proteins having a pI in the range of 6.5 to 9.5 are referred to as Pool 2 proteins (page 12). A delayed type hypersensitivity reaction to Pool 2 proteins (pI within the range of 6.5 to 9.5) was observed in a schizophrenic patient and no DTH reaction to Pool 1 proteins (pI within the range of 2 to 6.5) at the site of injection (See page 13).

6. Claims 6-13 rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

The "the pI of said proteins or fractions thereof is *greater than about 6.5*" in Claims 6-9 represents a departure from the specification and the claims as originally filed.

The passages pointed out by applicant in the amendment filed 1/6/04 do not provide a clear support for the said phrase.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 6-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/13152 publication (or record, April 1997; PTO 1449) in view of Jankovic et al (J Immunol 135(2 suppl): 583s-587s, Aug 1985, PTO 892), Ovary *et al* (Adv Biol Skin 11: 103-21, 1971; PTO 892), and Rotman *et al* (Prog Neuropsychopharmacol Biol Psychiatry 7(2-3): 135-41, 1983; PTO 1449).

The WO 97/13152 publication teaches a method for preparing a reagent for diagnosis of dementia comprising the steps of obtaining blood from a number of individuals or individual such as demented patients or healthy normal subjects, isolating platelet from the said blood samples (See entire document, page 8 in particular), preparing a protein fraction from the reference platelet preparation comprising proteins such as 75 kD platelet protein and platelet associated antibodies against said 75 kD platelet protein by isoelectric focusing, (See page 10, abstract, summary of invention, in particular) wherein said proteins have a pI between 7 and 9, which is *greater than about* 6.5 (See page 12, Fig 4). The reference pI is within the claimed range of above 6.5 to about 9.5.

The claimed invention in claim 6 differs from the teachings of the reference only that the method for the preparation of a reagent for use in diagnosis of schizophrenia instead of dermentia by obtaining blood sample from a number of individuals, collecting platelets from the pool of blood samples, preparing proteins fraction from said platelets wherein the pI of the said proteins or fractions thereof is greater than or equal to about 6.5.

The claimed invention in claims 7 and 9 differs from the teachings of the reference only that the diagnostic method for determining schizophrenia instead of dementia in an individual by obtaining a platelet protein preparation comprising platelet derived proteins wherein the pI of said proteins is greater than or equal to about 6.5, injecting into a subject said platelet proteins and examining the subject for the occurrence of delayed type hypersensitivity reaction at the site of injection, a positive result being a reaction above that which is observed in non-schizophrenic subjects, indicating that the subject ahs a high likelihood of being schizophrenic.

Jankovic *et al* teach a diagnostic method for determining schizophrenia in a subject by detecting a delayed type hypersensitivity reaction to a human brain antigen such as brain S-100 protein and the high incidence of positive skin DTH reaction to the reference protein in schizophrenia indicates that cell-mediated immune processes may be involved in schizophrenia (See abstract, in particular).

Ovary *et al* teach that the principal reason for the use of skin as a tool to study immunological phenomena because of its convenience. Skin has been used for decades to study allergic and immunologic response because skin reactions are easy to produce and observe and in many cases can be extremely sensitive in demonstrating sensitization (See page 103, 1st paragraph, in particular).

Rotman *et al* teach blood platelets are a very good model for nerve endings, serotonin uptake and imipramine binding and the efficiency of various drugs such as antidepressants have been evaluated using blood platelets instead of synaptosomes (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a protein fraction from platelets wherein protein fractions having a pI between 7 and 9 as taught by the WO 97/13152, and substituting the brain S-100 antigen taught by Jankovic et al for the platelet proteins fractions as taught by the WO 97/13152 and Rotman et al for a method of diagnosing schizophrenia in an individual by detecting a DTH as taught by Jankovic *et al* and Ovary *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Ovary *et al* teach that the principal reason for the use of skin as a tool to study immunological phenomena because of its convenience. Skin has been used for decades to study allergic and immunologic response because skin reactions are easy to produce and observe and in many cases

can be extremely sensitive in demonstrating sensitization (See page 103, 1st paragraph, in particular). Rotman *et al* teach blood platelets are a very good model for nerve endings, serotonin uptake and imipramine binding and the efficiency of various drugs such as antidepressants have been evaluated using blood platelets instead of synaptosomes (See abstract, in particular). Kessler *et al* teach platelets from schizophrenic patients bear autoimmune antibodies that inhibit dopamine uptake and that platelets could possibly serve as the peripheral trigger for an autoimmune reaction that eventually propagates to the CNS (See abstract, page 300, column 1, 1st paragraph, in particular). Jankovic *et al* teach that a high incidence of positive skin DTH reaction indicates that cell-mediated immune processes may be involved in schizophrenia (See abstract, in particular).

10. No claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

13. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.
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April 19, 2004

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